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Perinatal Toxicity of Endrin in Rodents
II. Fetotoxic Effects of Prenatal
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PERINATAL TOXICITY OF ENDRIN IN RODENTS. II. FETOTOXIC EFFECTS OF PRENATAL EXPOSURE IN RATS AND MICE

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SUMMARY

The fetotoxic potential of endrin in the CD rat and CD-1 mouse was investigated. Endrin was administered as a solution in corn oil to groups of pregnant animals by gastric intubation at multiple dose levels throughout the period of organogenesis. The dams were sacrificed prior to term and the fetuses were examined for skeletal and visceral anomalies. In addition, maternal livers and fetuses from rats in each dose level were analyzed for endrin content. In the mouse, endrin caused maternal liver enlargement at a dose of 0.5 mg/kg/day and reduced maternal weight gain at a dose of 1.0 mg/kg/day. Fetal weight and skeletal and visceral maturity were adversely affected at a dose of 1.0 mg/kg/day, but no teratogenic effect or embryo lethality was evident even at a dose level that produced maternal lethality (1.5 mg/kg/day). In the rat, endrin markedly reduced maternal weight at doses above 0.150 mg/kg/day but produced no apparent effects on the fetus. The data suggest that species differences in sensitivity to endrin may in part be due to differences in metabolism. Although endrin levels in rat fetuses at a maximally tolerated dosage level resembled those previously reported for the hamster, relatively less 12-ketoendrin was present, paralleling the change in fetal sensitivity.

INTRODUCTION

Endrin (1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-

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1,4-*endo*-5,8-dimethanonaphthalene) is one of the few cyclodiene pesticides still registered for use in the United States. Other members of this class of pesticides (aldrin, dieldrin, chlordane, and heptachlor) have been removed from the market or have had their uses restricted due to their high acute toxicity, environmental persistence, and/or carcinogenicity. Major uses of endrin have included that of an avicide, rodenticide, and insecticide. Following oral administration to rats, endrin is rapidly absorbed in the gastrointestinal tract. Endrin undergoes hepatic microsomal mono-oxygenase hydroxylation to yield mainly *anti*-12-hydroxyendrin, which is secreted via the bile as a glucuronide. Small amounts of *anti*-12-hydroxyendrin undergo rapid oxidation to 12-ketoendrin [1]. The metabolite appears to be the acute toxicant following exposure to endrin. The acute oral LD₅₀-values in the female rat are 5.3 mg/kg for endrin, 5.5 mg/kg for *anti*-12-hydroxyendrin, and 0.8 mg/kg for 12-ketoendrin [2]. Toxic effects appear to be mediated primarily through the central nervous system, as signs include ataxia, tremors and convulsions. The half-life of endrin in the rat is dependent upon the dose, requiring about 2 days for 16 µg/kg and about 6 days for 128 µg/kg [3].

The administration of 5 ppm of endrin in the diet of mice beginning 30 days prior to mating resulted in significant parental mortality and decreased litter sizes at birth [4], while administration of 2 ppm to rats for 3 generations had no effect on fertility, gestation, viability, and lactation indices [5]. Ottolenghi et al. [6] reported that single oral doses of endrin in hamsters at 5 mg/kg (one-half the LD₅₀ level) on days 7, 8 or 9 of gestation resulted in fetal death, reduced fetal weight, open eyes, and cleft palate. No significant effects on fetal weight or mortality were noted in mice treated on day 9 of gestation with a comparable dose, although the occurrence of open eyes was significantly elevated. Chernoff et al. [7] exposed hamsters to either a single oral dose of 0.5–10 mg/kg of endrin on day 8 of gestation (the acute oral LD₅₀ in non-pregnant hamsters was identified as 18 mg/kg) or to daily doses of 0.75–3.5 mg/kg/day from days 5–14 of gestation. Significant incidences of meningoencephaloceles at doses above 1.5 mg/kg and fused ribs above 5 mg/kg were found subsequent to the acute exposure regimen. The daily dosage regimen proved considerably more toxic to the dams (almost 40% of the dams receiving 1.5 mg/kg/day died during the period of administration) but produced fetal death and growth retardation rather than teratogenicity.

This study was undertaken in order to investigate the potential of endrin to induce developmental toxicity when administered throughout the period of organogenesis in the rat and mouse and to compare tissue levels of endrin in fetuses from the different species.

MATERIALS AND METHODS

Technical grade endrin (Lot 3112-3), supplied by Velsicol Chemical Corporation (341 East Ohio Street, Chicago, Illinois 60611), was reported

to be >99% pure. Time pregnant CD rats (approx. 175–200 g) and CD-1 mice (approx. 28–32 g) were obtained from Charles River Breeding Laboratory, Wilmington, Massachusetts. Day 1 of pregnancy was recorded upon demonstration of sperm in a vaginal smear (rats) or by the presence of a sperm plug (mice).

Endrin was dissolved in corn oil and administered via gastric intubation. The intubation volume was 0.1 ml/day for mice and 0.2 ml/day for rats. Control animals received the vehicle alone and all animals were treated between 9 a.m. and 11 a.m. The average maternal weight on day 6 was used for the calculation of doses. Mice were treated on gestation days 7–17 and rats on days 7–20. Dosages were selected following range finding studies in which non-pregnant adult females received endrin according to the treatment regimen prescribed for the teratology studies and information was recorded regarding the weight change of survivors and the number of doses to death for non-survivors. Due to the reported central nervous system toxicity of endrin, 30-min reactive locomotor activity levels (see Ref. 8 for details of the apparatus) were obtained after the first dose in rats and after the first, third and tenth doses in mice. Mice in the teratology study were exposed to endrin levels of 2.0, 1.5, 1.0, 0.5 or 0 mg/kg/day. In the rat teratology study, dosages of 0.450, 0.300, 0.150, 0.075 and 0 mg/kg/day were used.

Mice and rats were killed on days 18 and 21 of gestation, respectively. The uterus was examined in situ for the number of live, dead, or resorbed fetuses. The uterus was then removed and weighed. The maternal weight gain was calculated as the difference between the overall weight gain during pregnancy and the gravid uterus weight. The fetuses were removed from the uterus, blotted, weighed as a group, examined for gross anomalies, and divided equally for fixation in Bodian's solution (5% formaldehyde, 5% glacial acetic acid, and 70% ethanol) or 70% ethanol. The former were necropsied [9], and the latter were stained with alizarin red S and examined for skeletal abnormalities and maturity. The indicators of skeletal maturity used have been detailed previously [6]. All fetuses were examined on an experimenter-blind basis.

In the rat, the maternal liver and 1 fetus from each of 5 litters in each treatment group were analyzed by gas-liquid chromatography for endrin residues. Briefly, all residue analyses were performed on a Tracor 222 gas chromatograph equipped with a pulsed nickel-63 electron capture detector and a 183 cm × 4 mm inner diameter glass column packed with 1.5% OV-17 plus 1.95% OV-210 on 80/100 mesh Gas-Chrom Q. The presence of endrin and 12-ketoendrin, a metabolite, was confirmed in pooled tissue extracts using a Hewlett-Packard 5930A mass spectrometer. The identification of the compounds was supported by comparison with a standard in the case of endrin, and by comparison with spectra listed in the EPA/NIH Spectra Data Base [10]. No quantitative determination of the amount of 12-ketoendrin present in the tissues was possible due to lack of an authentic standard. Therefore, in order to compare the data we obtained in this experiment

with the rat to that obtained previously from the hamster, we used the ratio of the peak height of 12-ketoendrin to the peak height of endrin to obtain information on the relative amounts of metabolites present in the 2 species. Complete details of the procedures used and the mass spectra obtained have been reported previously [7].

Data are presented in the tables as the mean plus or minus the standard error of the mean. The litter was regarded as the fundamental unit of comparison in the statistical procedures. Analysis of variance was used to test for the presence of treatment effects. Percentage data were analyzed after arcsine transformation. When a significant effect of treatment was found, the significance of individual dosage groups was determined by the Least Significant Difference test.

RESULTS

Mouse

Toxicity study. Results of the preliminary range finding study are presented in Tables I and II. Doses of 1.5 mg/kg/day or greater resulted in decreased locomotor activity levels, reduced weight gain and lethality. Only 1 of 8 animals in the 1.5 mg/kg/day dosage group died as a result of endrin administration, but the survivors gained only 54% as much weight as did the controls. It is interesting to note that the animals in this group had apparently compensated for at least some of the observed behavioral toxicity by the end of the exposure regimen. While activity levels for those animals were significantly depressed after the first and third doses ($P < 0.01$), no significant difference in activity levels was apparent after the tenth dose.

Teratology study. Administration of endrin to CD-1 mice during the period of organogenesis resulted in dose-related indications of maternal

TABLE I

RESULTS OF PRELIMINARY RANGE FINDING STUDIES

Species	No. doses admin.	Dose levels (mg/kg/day)	No. died/No. treated	Avg. No. doses to death for non-survivors	Avg. wt change for survivors (g)
Mouse	11	0	0/8	—	3.9
		0.5	0/8	—	3.5
		1.5	1/8	6	2.1
		4.5	8/8	2.3	—
Rat	14	0	0/6	—	32.4
		0.5	3/5	7.7	1.8
		1.0	6/6	5.5	—
		2.0	9/9	3.4	—
		4.0	6/6	1.3	—

TABLE II

REACTIVE LOCOMOTOR ACTIVITY LEVELS IN ENDRIN TREATED NON-PREGNANT FEMALES^a

Species	No. of doses prior to testing	Dose (mg/kg/day)			
		0	0.5	1.5	4.5
Mouse	1	467 ± 22(8) ^b	448 ± 25(8)	290 ± 44(8) ^c	207 ± 45(7) ^c
	3	481 ± 31(8)	423 ± 30(8)	260 ± 24(8) ^c	—
	10	471 ± 40(8)	449 ± 32(8)	388 ± 48(7)	—
		0	0.5	1.0	2.0
Rat	1	665 ± 82(6)	400 ± 33(5) ^d	186 ± 49(6) ^e	83 ± 51(4) ^c

^a Activity levels were recorded in "figure eight" mazes [8] for a 30-min period that began 2–4 h after the animals had been dosed.^b Values are the mean number of photocell beam interruptions during a 30-min period ± S.D., the number of animals tested is given in parentheses.^c Significantly less active than controls, $P < 0.01$ by a Least Significant Difference Test.^d Significantly less active than controls, $P < 0.025$ by a Least Significant Difference Test.

toxicity, including death, decreased weight gain during pregnancy, and increased liver/body weight ratios (Table III). Viability at the highest dose level was so low (10%) that this dosage group was eliminated from the statistical analyses due to the small sample size.

No effect of endrin treatment was apparent on embryonic survival, but fetal weight was reduced in a dose-related fashion ($P < 0.01$). Dosage groups above 0.5 mg/kg/day were individually affected. This decrease in fetal weight was reflected in dose-related changes in the number of caudal vertebrae ($P < 0.05$), in the ossification of the supraoccipital ($P < 0.01$), and in the development of the renal pelvis ($P < 0.05$). These indicators of fetal maturity were not significantly different from control values for doses below 1.0 mg/kg/day. No dose-related occurrences of skeletal or soft tissue anomalies were observed.

Rats

Toxicity study. Results of the preliminary range finding study are presented in Tables I and II. The lowest dose tested (0.5 mg/kg/day) resulted in a 40% depression ($P < 0.025$) in activity levels after the first dose and eventual mortality for 3 of the 5 animals. Higher dosages resulted in a greater depression in activity levels and accelerated times to death. Activity level of animals in the 1.5 mg/kg/day group was only 28% of the control level. Two of the 6 animals in the 4.0 mg/kg/day group were in convulsions when the activity measurements were made (2–4 h after dosing) and were not tested. The remaining 4 animals had activity levels 88% lower than the controls.

TABLE III
RESULTS OF ADMINISTRATION OF ENDRIN TO MICE DURING ORGANOGENESIS^a

Observation	Dose (mg/kg/day)				
	0	0.5	1.0	1.5	2.0 ^f
Conception					
No. inseminated	40	38	39	20	20
No. died	0	0	0	4	18
No. pregnant (term)	27	31	32	12	2
Maternal					
Weight change (g) ^c	3.8 ± 0.3	3.7 ± 0.2	2.9 ± 0.2 ^d	2.0 ± 0.4 ^e	0.9
Liver/body wt (%) ^c	6.7 ± 0.2	7.2 ± 0.1 ^e	7.4 ± 0.1 ^e	8.1 ± 0.2 ^e	7.5
Fetal					
No. implants	10.2 ± 0.7	11.2 ± 0.5	11.8 ± 0.4	11.5 ± 0.5	14.0
% mortality	6.2 ± 2.4	9.4 ± 2.4	8.2 ± 1.3	2.2 ± 1.2	10.0
Fetal wt (g) ^c	1.08 ± 0.03	1.08 ± 0.03	0.99 ± 0.02 ^e	0.95 ± 0.03 ^e	0.87
No. sternebrae	5.9 ± 0.1	5.9 ± 0.1	5.7 ± 0.1	5.7 ± 0.1	5.7
Supraoccipital score ^c	1.3 ± 0.1	1.5 ± 0.1	1.8 ± 0.1 ^e	2.0 ± 0.2 ^e	2.3
No. caudal vertebrae ^b	4.5 ± 0.3	4.5 ± 0.2	3.8 ± 0.2 ^e	3.7 ± 0.4 ^d	3.7
% supernumerary ribs	13.8 ± 4.5	11.9 ± 3.3	13.2 ± 2.8	11.7 ± 4.0	28.6
Lateral ventricle score ^g	1.6 ± 0.1	1.6 ± 0.1	1.7 ± 0.1	1.8 ± 0.1	1.3
Renal pelvis score ^g	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	1.4 ± 0.1 ^d	1.4

^a Data presented as the mean ± S.E.M. The litter was used as the fundamental unit of comparison.

^b Significant treatment-related effect, $P < 0.05$, analysis of variance.

^c Significant treatment-related effect, $P < 0.01$, analysis of variance.

^d Significantly different from control value, $P < 0.05$, Least Significant Difference Test.

^e Significantly different from control value, $P < 0.01$, Least Significant Difference Test.

^f Excluded from the statistical analyses due to the reduction in sample size from maternal mortality.

^g See Chernoff et al. [7] for description of scoring technique.

TABLE IV
RESULTS OF ADMINISTRATION OF ENDRIIN TO RATS DURING ORGANOGENESIS^a

Observation	Dose (mg/kg/day)				
	0	0.075	0.150	0.300	0.450
Conception					
No. inseminated	32	15	28	30	15
No. died	0	0	0	0	0
No. pregnant	29	14	27	29	12
Maternal					
Weight change (g) ^b	69.0 ± 4.0	73.0 ± 3.0	66.8 ± 3.8	42.9 ± 4.9 ^c	8.8 ± 5.6 ^c
Liver/body wt (%)	4.7 ± 0.1	4.7 ± 0.1	4.7 ± 0.1	4.6 ± 0.1	4.6 ± 0.2
Fetal					
No. implants	11.5 ± 0.5	11.1 ± 0.7	12.3 ± 0.4	11.7 ± 0.6	11.6 ± 1.0
% mortality	6.9 ± 2.0	7.3 ± 1.5	7.2 ± 1.6	5.9 ± 2.0	9.0 ± 5.4
Fetal wt (g)	3.94 ± 0.08	4.02 ± 0.17	3.94 ± 0.06	4.01 ± 0.10	3.85 ± 0.11

^a Data are presented as the mean ± S.E.M. The litter was used as the fundamental unit of comparison.

^b Significant treatment-related effect, $P < 0.01$, analysis of variance.

^c Significantly different from control value, $P < 0.01$, Least Significant Difference Test.

TABLE V

ENDRIN LEVELS PRESENT IN MATERNAL LIVER AND FETUS OF THE RAT ON DAY 21 OF GESTATION FOLLOWING EXPOSURE ON DAYS 7-20

Dose (mg/kg/day)	Maternal liver (ppb)	Fetus (ppb)
0.150	63 (52-74) ^a	≤5 (<5-8)
0.300	68 (39-96)	≤5 (<5-6)
0.450	327 (261-323)	27 (13-42)

^aData presented as mean (range), there were 3 maternal livers and 6 fetuses (non-siblings) analyzed at each dose level. No endrin residues were present in similar numbers of control tissues.

Teratology study. Administration of endrin to CD rats during the period of organogenesis (Table IV) resulted in a marked dose-related reduction in maternal weight gain ($P < 0.01$). No change in the maternal/liver body weight was observed. There was no evidence that endrin affected fetal development. Fetal mortality, weight, degree of skeletal and visceral maturation and incidences of skeletal and visceral anomalies showed no dose related effects.

The results of analysis of endrin levels in maternal liver and fetus are presented in Table V. Hepatic tissue levels in the dams were similar for the 2 lower dosage groups, and rose to 327 ppb for dams receiving 0.450 mg/kg/day. Fetal tissue burdens ranged from the level of detection (5 ppb) in the 2 lower dose levels to a mean of 27 ppb in the 0.450 mg/kg/day dosage group. A metabolite identified by mass spectrometry as 12-ketoendrin was detected in samples but could not be quantified due to the lack of availability of an authentic standard. The peak height of 12-ketoendrin relative to endrin was 0.19 (range 0.08-0.47) for maternal livers and 0.35 (range 0.07-0.71) for the fetus. There was no relationship between dosage level and the ratio of the peak height of 12-ketoendrin to endrin.

DISCUSSION

Endrin is not teratogenic in the rat or mouse when administered at maternally toxic dose levels throughout the period of organogenesis. In particular, we saw no dose-related evidence of open eyes and cleft palate as reported earlier [6] in mouse fetuses exposed to an acute dose of 2.5 mg/kg endrin. Endrin, however, was fetotoxic in the mouse, as evidenced by dose-related decreases in fetal weight and of skeletal and visceral maturation. The dosage levels that produced fetotoxicity also produced maternal toxicity, indicating similar susceptibility for the adult female mouse and the fetus. In a previous study [7], a similar relationship between maternal toxicity and fetotoxicity was observed when hamsters were treated with endrin throughout the period of organogenesis. In the rat, however, a dose (0.450 mg/kg/day) that produced an 87% decrease in maternal weight gain had no apparent effect on

TABLE VI

SUMMARY OF ENDRIN TISSUE LEVEL DATA ON THE HAMSTER AND RAT FOLLOWING THE MAXIMUM TOLERATED DOSE THROUGHOUT GESTATION

Species	Maximum tolerated ^a dose (mg/kg/day)	Endrin concn. (ppb)		12-Ketoendrin/ endrin peak height ratio in fetus	Fetal effect
		Maternal liver	Fetus		
Hamster ^b	1.5	1450 ± 50(2) ^c	21 ± 4(10)	3.2 ± 0.6(10)	Growth retardation and lethality
Rat	0.450	327 ± 50(3)	27 ± 3(6)	0.4 ± 0.1(6)	No effect

^aHamsters were treated on days 5–14 of gestation and killed on day 15. Rats were treated on days 7–20 of gestation and killed on day 21.

^bHamster data from [7].

^cData presented as mean ± S.E.M. (No. of samples).

the fetus, indicating that this species' response to endrin was not similar to the other rodents tested. It should also be noted that maternal toxicity in the mouse is not necessarily associated with fetotoxicity. Using the same experimental protocol as in this study, decamethrin was administered at dose levels up to that which produced a 58% reduction in maternal weight gain without any concomitant fetal growth retardation [11].

Tissue levels of endrin in the rat and hamster at maximally tolerated dose levels are summarized in Table VI. Concentrations of endrin present in the maternal livers were proportional to the maximally tolerated dose. Fetal concentrations of endrin, however, were not proportional to the maximally tolerated dose levels, as both the hamster fetus and rat fetus had similar endrin content. Of special interest is the ratio of the peak height of 12-ketoendrin, a metabolite of endrin, to that of the parent compound in fetuses. This ratio averaged 3.2 in the hamster fetus compared with only 0.4 in the rat fetus. Thus, in the species in which endrin administration resulted in fetal mortality and reduced fetal weight (the hamster), similar amounts of endrin and relatively greater amounts of 12-ketoendrin were present compared with a species in which no effects on the fetus could be demonstrated (the rat). It is known that 12-ketoendrin is considerably more toxic to the adult than is endrin [2], and it appears from this study that the same sensitivity holds true for the fetus.

These results demonstrate that there are marked species differences in the effects of endrin on rodent development. Adult female rats tolerate 2–3 times less endrin than do adult female mice or hamsters, and yet the rat is the only one of the 3 species in which endrin did not induce fetotoxicity. Evaluation of tissue burden data for the hamster and rat indicated that the species differences may in part be due to differences in metabolism.

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